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In This Issue

Management of Central Venous Catheter Occlusions

Central venous cannulation has allowed the administration of life-saving therapies such as total parenteral nutrition (TPN), chemotherapy, antibiotics, and blood products. These therapies are commonly administered through central venous catheters to treat patients with a variety of conditions. There are several types of central venous catheters, including those that are tunneled, nontunneled, or implanted; those that are open-ended or closed-tipped; and those with single or multiple lumens. While these devices provide substantial benefits, they are sometimes associated with complications that can occur shortly after insertion, during long-term use, or upon removal of the device.

Catheter-related thrombosis is a major complication affecting central venous catheters and can result in an impaired ability to withdraw fluid from or infuse fluid through the catheter. The incidence of catheter-related thrombosis reportedly ranges from 3 percent to 70 percent. This broad range reflects the varying definitions used in the literature and the lack of a standardized method for evaluating and diagnosing this condition. The term catheter-related thrombosis may refer to the thrombotic occlusion of a catheter, the formation of a fibrin sheath around the catheter, the formation of a small thrombus at the site of catheter insertion into the vessel, or a true thrombosis within the central vein. The latter condition also has been termed catheter-related venous thrombosis.

Catheter-related thrombosis can be managed by replacing the catheter or restoring its patency. Whenever possible, an attempt should be made to salvage the catheter.

Urokinase (Abbokinase; Abbott Laboratories) has been shown to be effective for salvaging thrombosed central venous catheters. Due to concerns about potential contamination of urokinase, "FDA has informed Abbott Laboratories of additional concerns related to manufacturing deficiencies for urokinase (Abbokinase). Until these problems are corrected, further distribution of Abbokinase would violate federal laws designed to assure the safety of drugs for patient use."

The resultant shortage of urokinase has created an urgent need for alternative thrombolytics for the management of occluded central venous catheters. Both streptokinase and alteplase have been used to restore patency of occluded catheters. Streptokinase is a bacterial protein known to be highly antigenic in humans. The formation of antibodies to streptokinase may limit its subsequent use. Unlike streptokinase, urokinase and alteplase have a low potential for immunogenicity. Antibodies directed against alteplase are rare. Anaphylactoid reactions to alteplase are uncommon and to date only one case of anaphylaxis has been reported. Preliminary data suggest that alteplase may be an effective alternative to urokinase for the treatment of catheter-related thrombotic occlusions.

Central Venous Catheter Complications

Thrombotic obstruction of the catheter and catheter-related infection (local or systemic) are the most commonly reported complications of central venous catheters. Other complications include nonthrombotic occlusions, venous thrombosis, and catheter migration or malpositioning. Catheter occlusions can be complete or partial. Partial occlusions generally manifest as an ability to infuse but not aspirate fluid through the catheter. An occlusion can occur soon after insertion of the device or during prolonged use of the catheter.

Catheter complications can be multifactorial. For example, drug precipitates in the catheter may occur in conjunction with thrombus formation. Since this may have implications for management of the occlusion, the possibility of a drug precipitate or other

nonthrombotic obstruction always should be considered during assessment of the occlusion.

Catheter Occlusions

Nonthrombotic Occlusions: Nonthrombotic occlusions may reflect mechanical obstruction, drug or mineral precipitates, or lipid residue. Mechanical obstruction can be caused by kinked or clamped tubing, a clogged in-line filter, an improperly placed port-access device, or from overly restrictive securing sutures. Additional examples of mechanical malfunction include catheter migration or malpositioning and pinch-off syndrome. In many instances, these problems are easy to identify and correct, and should be ruled out first.

The tip of a central venous catheter should reside in the lower one third of the superior vena cava (SVC) at the right atrial juncture. Despite optimal catheter tip placement in the SVC (as verified by chest X-ray), catheters can migrate or become malpositioned during insertion and use. Factors influencing the incidence of malposition include an increase in intrathoracic pressure from coughing, sneezing, or vomiting; arm movements; forceful flushing of the catheter; and thrombus formation. Often, malpositioned catheters are needlessly removed despite the availability of safe and effective repositioning techniques. Possible interventions to reposition catheters include patient positioning, rapid flushing of the catheter guidewire catheter exchange, fluoroscopic catheter guidance, partial catheter withdrawal, or use of a thrombolytic (if malpositioning is caused by a thrombus).

Precipitates can form as a result of drug crystallization, drug-drug incompatibilities, or drug-solution incompatibilities. Treatment of drug precipitates largely depends on whether they are likely to solubilize with a change in pH. Hydrochloric acid (0.1 N) is used for substances known to dissolve in an acidic medium. Sodium bicarbonate (1 mEq/mL) is used for substances known to dissolve in an alkaline environment. Catheters occluded by calcium-phosphate precipitates can be treated effectively with 0.1 N hydrochloric acid. Obviously, the use of incompatible drugs or solutions should be avoided. Lipid residue also can accumulate in central venous catheters. This often follows the administration of lipid-containing, three-in-one TPN admixtures or drugs with oleaginous vehicles. Lipid occlusions have been treated with ethanol (70 percent) or sodium hydroxide (0.1 mmol/mL). Repeated occlusion following treatment with a thrombolytic agent may indicate the presence of one or more of these types of occlusions.

Thrombotic Occlusions: The primary cause of catheter occlusion is the formation of a thrombus within or surrounding the catheter. The catheter tip is the most common site of catheter occlusion. Thrombotic occlusion of the catheter can impair the ability to infuse fluid through and/or aspirate fluid from the catheter. Knowledge of the factors that lead to catheter occlusions is critical for their optimal identification, assessment, and management.

Types of Occlusions

There are several sites at which thrombi are likely to form: the lumen of the catheter, the site where the catheter enters the vein, the catheter tip, and the external surface of the catheter. The types of thrombotic occlusions include intraluminal thrombus, mural thrombus, fibrin sheath (also known as fibrin sleeve), and fibrin tail (also known as fibrin flap). Intraluminal thrombus forms within the lumen of the catheter and may result in a partial or complete occlusion. A fibrin sheath forms when fibrin adheres to the external surface of the catheter and may resemble a sock over the catheter. Fibrin tail forms when fibrin adheres to the end of the catheter. Often it acts as a one-way valve, permitting infusion but not withdrawal of fluid from the catheter. Mural thrombus forms when the fibrin from a vessel-wall injury binds to the fibrin covering the catheter surface and may lead to the formation of a venous thrombus.

Risk Factors

Patients at greatest risk for the development of catheter-related thrombosis are those who experience venous stasis, enhanced blood coagulability, or trauma to the vessel wall. Venous stasis can occur when dehydration, hypotension, immobility, heart failure, or intrapulmonary/mediastinal disease are present. Coagulability can be altered by such conditions as malignancy, sepsis, chronic renal failure, or the administration of chemotherapy. Unfortunately, these characteristics are common to many patients who require central venous access.

Trauma to the vessel wall can result from insertion and residence of the catheter or from infusion of intravenous solutions. The specific method and ease of catheter insertion, as well as catheter size, flexibility, position, material composition, and duration of catheter use can influence the degree of vessel trauma. Catheters with left-sided placement and with malpositioned catheter tips pose a high risk for thrombus development. Polyvinylchloride and polyethylene catheters are more thrombogenic than the newer polyurethane and silicone catheters. Because of their rigid construction and relatively high displacement of blood flow, larger-diameter catheters are more likely to cause trauma to the vessel or obstruct flow than catheters of smaller diameter.

Signs and Symptoms

The vast majority of thrombi related to central venous catheters develop without symptoms. Warning signs are insidious but can be recognized by experienced clinicians. As the thrombus begins to form, the catheter may seem sluggish or otherwise problematic. As thrombus formation progresses, infusion pump alarms may sound frequently or visible clots may appear on the exterior portion of the catheter. In some instances, particularly when a fibrin sheath forms over the catheter tip, it may be possible to infuse fluid into the catheter, but fluid withdrawal is impaired (e.g., ball-valve effect). The diagnosis of catheter-related thrombosis may be based solely on symptoms or can be confirmed with the aid of imaging techniques.

Salvaging the Occluded Catheter

When a central venous catheter becomes occluded, the ultimate goal is to restore patency in a timely and cost-effective manner with minimal risk to the patient. In many cases, catheter salvage is preferred over catheter replacement for several reasons. These include limited interruption of

therapy, reduced risk of trauma to the patient, reduced risk for complications, and decreased cost.

Treatment of Central Venous Catheter Occlusions With Alteplase

Alteplase is a recombinant form of the naturally occurring tissue plasminogen activator that enhances the conversion of plasminogen to plasmin in the presence of fibrin. When introduced into the systemic circulation at pharmacologic doses, alteplase binds to the fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This action initiates local fibrinolysis, with limited systemic proteolysis. Currently, alteplase is FDA-approved for the management of acute myocardial infarction, acute ischemic stroke, and acute massive pulmonary embolism. It is not FDA-approved for the treatment of occluded central venous catheters. The results of several published clinical studies suggest that alteplase may be effective for the management of occluded central venous catheters.

Atkinson and colleagues conducted a study to evaluate the efficacy of urokinase and alteplase for the treatment of occluded central venous catheters. Occlusions were initially treated with urokinase. Six of 25 occlusions failed to resolve after an initial 10,000-U dose of urokinase. These six occlusions were treated with a 2-mg dose of alteplase instilled into the catheter for a 4-hour dwell time. Alteplase restored catheter patency in five of the six catheters. There was no evidence of fibrinogen breakdown or bleeding diathesis in any of the patients.

Haire et al conducted a double-blind, randomized clinical trial comparing urokinase and alteplase for the treatment of thrombosed central venous catheters. A total of 50 occluded catheters, as confirmed by radiographic contrast injection, were treated with urokinase 10,000 U (n=22) or alteplase 2 mg (n=28) for a 2-hour dwell time. For each drug, the total volume per dose was 2 mL. A second dose of drug was permitted if catheter function was not restored after the initial dose.

The results of this study demonstrated that alteplase-treated catheters were significantly more likely to experience a return of function (25/28, or 89 percent) than urokinase-treated catheters (13/22, or 59 percent; P=0.013). Radiographic contrast injection confirmed the complete resolution of the occlusion in nearly twice as many alteplase-treated catheters (17/28, or 61 percent) as urokinase-treated catheters (7/22, or 32 percent; P=0.042). In addition, fewer of the urokinase-treated catheters (4/22, or 18 percent; P=0.036) experienced restored patency after just one dose of drug compared with the alteplase-treated catheters (13/28, or 46 percent). No complications such as bleeding, embolization, or septicemia were observed in either treatment group.

Although randomized clinical trials are unavailable, isolated reports also suggest that alteplase may be effective for clearance of occluded dialysis catheters.

Safety

The most common adverse event associated with the systemic administration of alteplase is bleeding. Systemic doses of alteplase used in acute myocardial infarction, pulmonary embolism, and stroke (i.e., up to 100 mg) are large in comparison to the lower doses used to lyse occluded catheters (i.e., 2 mg). Proper instillation of alteplase into the lumen of the catheter should result in minimal systemic drug exposure. The data published to date suggest that coagulation abnormalities and bleeding are unlikely in patients who receive small doses of alteplase for catheter clearance.

Dosage

The optimal alteplase dose, solution volume, and dwell time for the clearance of thrombosed central venous catheters have not yet been determined. Data from Haire et al suggest that a 2-mg dose (1 mg/mL) and a 2-hour dwell time may be appropriate. However, additional studies with smaller doses and shorter dwell times would be useful.

Preparation and Storage

Alteplase is supplied as a sterile, lyophilized powder in 50-mg (29 million IU) and 100-mg (58 million IU) vials. It should be noted that alteplase is preservative-free; therefore, it is essential that aseptic technique be utilized in the process of preparation, storage, handling, and administration. Once reconstituted with Sterile Water for Injection, USP to a concentration of 1 mg/mL, the alteplase solution should be used within 8 hours. Because only small doses of alteplase are needed for catheter clearance, preparation and freezing of small aliquots of alteplase may minimize drug waste and reduce overall cost.

A team of NIH investigators evaluated the bioactivity of a 1 mg/mL solution of alteplase that was either stored in polypropylene tubes at -20C for 6 months or in glass vials at -70C for 2 weeks. In both cases, the bioactivity of the frozen solutions, measured by a chromogenic assay, was nearly identical to that of freshly prepared alteplase. Genentech, Inc. conducted a similar in-house experiment employing a clot-lysis assay. Alteplase solutions (1 mg/mL) stored in glass vials at -20C were found to retain their full bioactivity for 32 days. Neither study, however, evaluated the frozen samples for the presence of pyrogens or microbial growth. It should be noted that alteplase solutions used in these experiments were stored in non-cycling freezers to avoid fluctuations in freezing temperatures.

Administration

Suggested procedures for treating partial and total thrombotic occlusions with alteplase have been developed. The appropriate volume of the alteplase solution should be based on the internal volume of the catheter (i.e., catheter dead space). For catheters requiring more than 2 mL of solution, the alteplase solution should be further diluted to the necessary volume only with preservative-free 0.9 percent NaCl.

Summary

Central venous catheters are valuable devices for administering life-saving therapies. Catheter-related thrombosis, a major complication affecting central venous catheters, may be managed by replacing the catheter or restoring its patency. Catheter salvage is the preferred approach for managing catheter occlusions.

Preliminary data suggest that alteplase may be an appropriate alternative to urokinase for the treatment of thrombotic catheter occlusions. Data from Haire et al data suggest that a 2-mg dose (1 mg/mL) and a 2-hour dwell time may be effective for restoring catheter patency.

The treatment of thrombosed catheters with alteplase continues to evolve. Several questions remain to be answered. Can a second instillation of alteplase restore patency if the initial instillation is not effective? What is the optimal alteplase dose, solution volume, and dwell time? Can alteplase be administered as a continuous infusion to restore patency of catheters refractory to initial treatment? Is there a role for alteplase in the treatment of catheter-related infection? Future studies are needed to answer these important questions.

References available upon request.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions:

- Cabergoline (Dostinex®), a dopamine agonist used for the management of hyperprolactinemia
- Conjugated estrogens/medroxyprogesterone (Prempro®)
- Levonorgestrel and ethinyl estradiol (Triphasil®)
- Norethindrone (Nor-QD®)
- Estradiol (Estrace®)
- Micronized progesterone (Prometrium®)
- Metronidazole vaginal cream (Metrogel®)
- Quetiapine (Seroquel®), an atypical antipsychotic
- Etanercept injection (Enbrel®), an inhibitor of tumor necrosis factor used for the treatment of severe rheumatoid arthritis
- Rosiglitazone (Avandia®), a thiazolidinedione antidiabetic agent
- Pioglitazone (Actos®), a thiazolidinedione antidiabetic agent
- Ofloxacin otic (Floxin®), a topical fluoroquinolone antibiotic
- Amphotericin B oral suspension (Fungizone®), an antifungal agent for azole-resistant candidiasis
- Fluticasone nasal inhaler (Flonase®), a glucocorticoid used for the treatment of seasonal and perennnial rhinitis
- Guaifenesin (Humibid LA®)
- Hypertonic (3%) buffered saline (Sinucleanse®), a nasal spray for osmotic nasal decongestion in patients with rhinosinusitis

Deletions:

- Beclomethasone (Vancenase®)

Editors' Note

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